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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Gauch et al.
Serial No.:	09/536,735
Filed:	March 28, 2000
Entitled:	ISOLATION OF NUCLEIC ACIDS ON SURFACES

ART UNIT: 1655

EXAMINER: B. Sisson

Attorney Docket No.: QGN-009.2 US

Commissioner for Patents  
Washington, D.C. 20231

**RESPONSE TO AN OFFICE ACTION UNDER 37 C.F.R. § 1.111**

Sir:

This paper is filed in response to the Office Action (Paper No. 10), dated March 12, 2002, in the above-identified application. Pursuant to 37 C.F.R. § 1.136(a), a Petition for a three-month extension in time is submitted concurrently herewith along with a check in payment of the fee under 37 C.F.R. § 1.17(a)(3).

A Supplemental Information Disclosure Statement is filed concurrently herewith.

Please amend the application as indicated below.

**IN THE CLAIMS**

Please cancel Claims 1-8, 14-19, and 77-95.

Please amend the claims as indicated below and in clean form pursuant to 37 C.F.R. § 1.121(c)(1)(i). A version of the amended claims with markings on a separate sheet pursuant to 37 C.F.R. § 1.121(c)(1)(ii) is also attached herewith at Appendix A, and a complete set of pending claims, as amended herein, pursuant to 37 C.F.R. § 1.121(c)(3) is attached herewith at Appendix B.

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Amended Claims in Clean Form Pursuant to 37 C.F.R. § 1.121(c)(i)

9. (twice amended) A process for the isolation of nucleic acids from a sample comprising the following steps:

- C<sup>1</sup>
- (a) applying at least one nucleic acid sample to a non-siliceous surface;
  - (b) immobilizing the nucleic acids of the nucleic acid sample on the non-siliceous surface in the presence of a compound selected from the group consisting of a salt of a metal and/or ammonium cation with a mineral acid, a salt of a mono or polybasic or polyfunctional organic acid with an alkaline or alkaline-earth metal, a hydroxy-functional compound of an aliphatic or acyclic saturated or unsaturated hydrocarbon, a phenol or polyphenol, a chaotropic agent, and combinations thereof, wherein the nucleic acids are reversibly immobilized on the non-siliceous surface;
  - (c) releasing the immobilized nucleic acids from the non-siliceous surface with an elution agent, characterized in that the release takes place at a temperature T, whereby  $10^{\circ}\text{C} \geq T \geq T_{S,EM}$ , and  $T_{S,EM}$  equals the freezing point of the elution agent.

C<sup>2</sup> 11. (amended) The process according to Claim 9, characterized in that the release takes place at temperature T, in which  $10^{\circ}\text{C} \geq T \geq 0^{\circ}\text{C}$ .

12. (amended) The process according to Claim 9, characterized in that the release takes place at temperature T, in which  $10^{\circ}\text{C} \geq T \geq -5^{\circ}\text{C}$ .

C<sup>3</sup> 20. (amended) The process according to Claim 9, characterized in that after the release step at least one additional step takes place:

- performing at least one chemical reaction with the nucleic acids.

C<sup>4</sup> 37. (amended) The process according to Claim 9, characterized in that the sample is introduced onto the top of the surface.

C<sub>4</sub> 38. (amended) A process according to Claim 9, characterized in that the immobilized nucleic acids are subjected to a washing step which takes place with at least one washing buffer after the immobilization and before any release steps.

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C<sub>5</sub> 39. (amended) The process according to Claim 38, characterized in that the washing step consists of the following steps for each washing buffer:

- applying a predetermined quantity of washing buffer on the non-siliceous surface; and
  - passing the washing buffer through the non-siliceous surface.
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40. (amended) The process according to Claim 9, characterized in that an aqueous salt or buffer solution is used to release the nucleic acids.

C<sub>6</sub> 41. (amended) The process according to Claim 9, characterized in that water is used to release the nucleic acids.

42. (amended) The process according to Claim 9, characterized in that the application and immobilization of the nucleic acids includes the following steps:

- mixing at least one nucleic acid-containing sample with an immobilization buffer;
- applying said at least one nucleic acid-containing sample with the immobilization buffer to the non-siliceous surface; and
- passing the liquid components through the non-siliceous surface in essentially the same direction they were added.

43. (amended) The process according to Claim 9, characterized in that at least one of the steps is carried out by an automatic device, in a fully automatic manner.

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C<sub>7</sub> 46. (amended) The process according to Claim 9, characterized in that aqueous salt solutions of metal and/or ammonium cations with mineral acids are used to immobilize the nucleic acids.

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C<sub>8</sub> 48. (amended) The process according to Claim 46, wherein the aqueous salt solution is selected from the group consisting of sodium halides, lithium halides, potassium halides, magnesium sulfate, and combinations thereof.

C<sub>9</sub> 49. (amended) The process according to Claim 9, characterized in that aqueous solutions of salts of mono or polybasic or polyfunctional organic acids with alkaline or alkaline-earth metals are used to immobilize the nucleic acids.

C<sub>10</sub> 54. (amended) The process according to Claim 9, characterized in that hydroxy-functional compounds of aliphatic or acyclic saturated or unsaturated hydrocarbons are used for the immobilization of the nucleic acids.

C<sub>11</sub> 58. (amended) The process according to Claim 9, characterized in that a phenol or polyphenol is used for the immobilization of the nucleic acids.

59. (amended) The process according to Claim 9, wherein at least one chaotropic agent is used for the immobilization of the nucleic acids.

C<sub>12</sub> 66. (amended) The process according to Claim 9, characterized in that the non-siliceous surface is a membrane.

C<sub>13</sub> 73. (amended) The process according to Claim 66, wherein the membrane is a hydrophilic membrane or a membrane made hydrophilic by pre-treatment.

C<sub>14</sub> 75. (amended) The process according to Claim 66, characterized in that the membrane has a pore diameter of 0.001 to 50 micrometer.

C<sub>15</sub> 112. (amended) The process according to Claim 9 wherein said surface comprises a material selected from the group consisting of cellulose acetate; non-carboxylized, hydrophobic polyvinylidene fluoride; and massive, hydrophobic polytetrafluoroethylene.

C<sub>16</sub> 125. (new) The process according to Claim 9 for the isolation of nucleic acids from a sample further comprising, prior to step (a), the step of adjusting said at least one nucleic acid sample to binding conditions that permit reversible immobilization to a non-siliceous surface, and wherein there is a pretreatment of said at least one nucleic acid sample before and/or after adjusting the binding conditions of said at least one nucleic acid sample.

126. (new) The process according to Claim 125, wherein said pretreatment is selected from the group consisting of salting out, filtration, centrifugation, enzymatic treatment, temperature adjustment, precipitation of non-nucleic acid material, extraction, homogenization, mechanical reduction, binding of contaminants to surfaces, and combinations thereof.

127. (new) The process according to Claim 125, wherein said binding conditions permit reversible immobilization of RNA.

128. (new) The process according to Claim 125, wherein said binding conditions permit reversible immobilization of DNA.

129. (new) The process according to Claim 9, wherein said non-siliceous surface is a material in the form selected from the group consisting of a membrane, a granulate, and a fiber.

REMARKS

Applicants have amended the claims of this application mainly to direct coverage to the preferred process of Applicants' invention for isolating nucleic acids in a sample, as recited in Claim 9, which *inter alia* comprises applying at least one nucleic acid sample to a *non-siliceous* surface, reversibly immobilizing the nucleic acids of the sample on the non-siliceous surface, and releasing the immobilized nucleic acids from the non-siliceous surface with an elution agent at a temperature  $T$ , whereby  $10^{\circ}\text{C} \geq T \geq T_{\text{S,EM}}$ , and  $T_{\text{S,EM}}$  equals the freezing point of the elution agent. The amendments also adjust dependencies of some of the claims, ensure consistent use of terms throughout the claims, and correct minor typographical errors. Applicants have therefore canceled Claims 1-8, 14-19, and 77-95; amended Claims 9, 20, 37-43, 46, 48, 49, 54, 58, 59, 66, 73, 75, and 112; and added new Claims 125-129. Applicants reserve the right to seek patent coverage for the subject matter of the canceled claims in a subsequent continuation application. The amendments described herein also render moot a number of rejections cited in the Office Action (Paper No. 10), mailed March 12, 2002, including rejections based on documents cited by the Examiner.

Claim 9 is directed to a process of Applicants' invention for the isolation of nucleic acids from a sample comprising applying at least one sample to a non-siliceous surface; reversibly immobilizing the nucleic acids of the sample on the non-siliceous surface in the presence of one or more compounds listed in step (b) of the claim; and releasing the immobilized nucleic acids from the non-siliceous surface with an elution agent at temperature  $T$ , whereby  $10^{\circ}\text{C} \geq T \geq T_{\text{S,EM}}$ , wherein  $T_{\text{S,EM}}$  equals the freezing point of the elution agent. As the Examiner recognized in the Office Action, the process of Claim 9 is not taught or suggested in any reference or combination of references cited in the Office Action. Support for the amendment to Claim 9 is found in original Claim 9 and the specification (see, e.g., p. 6, lines 20-p. 7, line 8 of the specification). The term "non-siliceous" was previously recited only in step (a) of Claim 9. The term "membrane" was inadvertently inserted into the last phrase of step (b) of Claim 9 when a specific list of compounds used for reversible immobilization of nucleic acids was inserted into the claim (see, Response (Paper No. 9), filed December 20, 2001). Accordingly, the amendment adds no new matter.

The amendment to Claim 10 provides a uniform recitation throughout the claim that nucleic acid is applied to, reversibly immobilized on, and released from a "non-siliceous surface", and thus adds no new matter.

Claims 11 and 12 were amended to correct an inadvertent typographical error. Specifically, the term "Claims 9" was recited in both claims and has now been corrected to read "Claim 9". Accordingly, the amendments add no new matter.

Particular embodiments of the process according to Claim 9 wherein the non-siliceous surface is a non-siliceous membrane is covered in the language of dependent Claim 66, amended herein to remove dependencies from canceled claims, and also in the Markush group of new Claim 129. New Claim 129 is directed to the embodiment of the process according to Claim 9 wherein the non-siliceous surface is a material that may be in any of several preferred forms, i.e., a membrane, a granulate, or a fiber. Support for the group of preferred forms recited in Claim 129 is found in the specification (see, e.g., p. 20, lines 6-7 of the specification). Accordingly, neither the amendment of Claim 66 nor new Claim 129 adds new matter.

Applicants have also amended Claims 20, 37, 38, 39, 40, 41, 42, 43, 46, 48, 49, 54, 58, 59, 66, 73, 75, and 77 to remove dependencies from canceled claims and to correct dependencies (directly or indirectly) to independent Claim 9. Accordingly, the amendments add no new matter.

Claims 39 and 42, which depend from Claim 9, were also amended to insert the term "non-siliceous" before "surface", consistent with the terminology and scope of independent Claim 9. Accordingly, the amendments add no new matter.

Claim 48 was amended to organize the recited species of aqueous salt solutions into a more familiar Markush-type claim. Applicant has also amended Claim 48 to depend from Claim 46, instead of Claim 46 (which, itself, depends from Claim 46). The dependency from Claim 46 is appropriate as Claim 48 clearly recites the use of preferred species of the genus of aqueous salt solutions of metal with mineral acids mentioned in Claim 46. The use of such species of aqueous salt solutions in the process of the invention is described in the specification (see, e.g., p. 17, lines 1-6 of the specification). Accordingly, the amendments improve the form of the claim and add no new matter.

Claim 112 (and thereby Claims 113-116) has been amended to depend from Claim 9. Claim 112 specifies that the non-siliceous surface in the process of Claim 9 may comprise any of

several particularly preferred materials and in various forms (dependent Claims 113-116) as described in the specification (see, e.g., p. 20, lines 1-7 of the specification). Accordingly, the amendment adds no new matter.

Applicants have also added new dependent Claims 125, 126, 127, 128, and 129. New Claim 129 is described above. New Claim 125 covers an embodiment of the process according to Claim 9, wherein the nucleic acid sample is adjusted to binding conditions to permit reversible immobilization on a non-siliceous surface wherein there is a pretreatment of the sample before and/or after adjusting the binding conditions, as previously recited in original Claim 14 (now canceled) and the specification (see, e.g., p. 23, lines 11-15 of the specification). Accordingly, new Claim 125 adds no new matter.

New Claim 126, which depends from new Claim 125, specifies preferred types of pretreatments that may be used alone or in combination with the claimed process as previously recited in original Claims 15 and 16 (both, now canceled). Accordingly, new Claim 126 adds no new matter.

New Claims 127 and 128 specify that the binding conditions in Claim 125 permit reversible immobilization of RNA and DNA, respectively, as previously mentioned in original Claims 16 and 17 (both now canceled). Accordingly, new Claims 127 and 128 add no new matter.

Entry of the amendments is respectfully requested.

#### Objection to Claim 2

In the Office Action, the Examiner objected to Claim 2 as being of an improper dependent form for failing to further limit the subject matter. Without acceding to the Examiner's view of Claim 2, Applicants have canceled Claim 2, thereby rendering the matter moot. Removal of the objection is respectfully requested.

#### Rejections Under 35 U.S.C. § 112, first paragraph

The Examiner rejected Claims 1-56, 58-75, 77-95, and 112-124 under 35 U.S.C. § 112, first paragraph, as lacking an enabling description. Applicants respectfully traverse the rejection for the reasons given below.



In the Office Action, the Examiner rejected Claims 9, 14, 77, and 112 and, thereby, claims depending therefrom, because certain limitations stated in independent Claim 1 were absent from independent Claims 9, 14, 77, and 112, such as using a "non-siliceous membrane". The Examiner also rejected Claims 1-8, 20, 38-56, 58-65, 73, 74, 121, and 122 apparently as overly broad, asserting that the claims lack a sufficient delineation of parameters, e.g., temperature, under which the claimed processes can be performed.

The claims of this application are now directed exclusively to Applicants' novel process for the isolation of nucleic acids from a sample according to the process of Claim 9. The process of Claim 9 is based on Applicants' discovery that nucleic acids may be reversibly immobilized on a non-siliceous surface and subsequently eluted from the non-siliceous surface with an elution agent at a temperature  $T$ , whereby  $10^{\circ}\text{C} \geq T \geq T_{\text{S,EM}}$ , and  $T_{\text{S,EM}}$  equals the freezing point of the elution agent, which is described in the specification (see, e.g., p. 6, line 25-p. 7, line 31 of the specification). Persons skilled in this art who read the specification would clearly understand the conditions necessary to carry out Applicants' process involving low temperature elution for isolating nucleic acids on a non-siliceous membrane. As noted above, Applicants have canceled independent Claims 1, 14, and 77; amended Claim 112 to depend from amended Claim 9; and eliminated dependencies from canceled claims. The claims now properly depend from and recite terms consistent with the process of amended Claim 9.

The above comments clearly show that independent Claim 9 and claims depending therefrom are supported by the specification in accordance with the requirements of 35 U.S.C. § 112, first paragraph. Accordingly, the Examiner is respectfully requested to reconsider and withdrawal the rejections.

Rejections Under 35 U.S.C. § 112, second paragraph, and 35 U.S.C. § 101

The Examiner also rejected Claims 112-116 under 35 U.S.C. § 112, second paragraph, as being indefinite and under 35 U.S.C. § 101 as an improper definition of a claimed process. In particular, the Examiner was of the view that Claims 112-116 failed to recite positive and essential steps for carrying out a method to achieve the stated goal of isolating nucleic acids.

As noted above, Applicants have amended Claim 112 (and thereby Claims 113-116) to specify particularly preferred embodiments of the process according to Claim 9, which clearly recites positive and essential steps for carrying out a process for the isolation of nucleic acids

(e.g., immobilization of nucleic acids on a non-siliceous surface and release of nucleic acids from the non-siliceous surface with an elution agent at a defined low range of temperature). Accordingly, Applicants respectfully submit that Claims 112-116 as amended herein clearly conform to the requirements of 35 U.S.C. § 112, second paragraph, and 35 U.S.C. § 101.

In view of the above comments, the Examiner is respectfully requested to reconsider and withdraw the rejections.

#### Rejections Under 35 U.S.C. § 102

In the Office Action, the Examiner rejected Claims 14-20, 37-50, 54, 55, 59-65, 76, 112, 115, 116, 121, and 122 as anticipated under 35 U.S.C. § 102 by Walter (US Patent No. 5,910,246). Claims 14-20, 37-42, 46-49, 54-56, 59-65, 112, 114, 121, and 122 were rejected as anticipated by Hofstetter (US Patent No. 5,081,028). Claims 1, 4, 6-8, 14, 16-20, 37-42, 46-49, 52, 53, 65, 73-75, 112, and 113 were rejected as anticipated by Comai (US Patent No. 5,187,267).

Applicants note that the rejections are directed to one or more combinations of independent Claims 1, 14, and 112, and claims depending therefrom. None of the rejections is directed to independent Claim 9 and its dependent claims, which cover Applicants' process for isolating nucleic acids comprising reversibly immobilizing nucleic acids on a non-siliceous surface and releasing the immobilized nucleic acids with an elution agent at a defined, low range of temperature. As noted above, Applicants have canceled independent Claims 1 and 14, amended Claim 112 to depend from Claim 9, and eliminated improper claim dependencies.

Without acceding in any way to the Examiner's view of the claims and cited patents, Applicants respectfully submit that the rejections under 35 U.S.C. § 102 are now moot, and respectfully request reconsideration and withdrawal of the rejections.

#### Rejections Under 35 U.S.C. § 103

The Examiner also rejected Claims 1-8, 14-20, 37-56, 58-76, 112-116, and 121-124 as obvious over Marquet (US Patent No. 5,561,064) in combination with Manesfield (US Patent No. 5,527,672) and Walter. As in the case of the rejections under 35 U.S.C. § 102, above, the rejections under 35 U.S.C. § 103 are directed to a combination of independent Claims 1, 14, and 112, and claims depending therefrom, but not to Claim 9. Since Applicants have canceled

independent Claims 1 and 14, amended Claim 112 to depend from Claim 9, and corrected improper dependencies, Applicants submit that the rejections under 35 U.S.C. § 103 are rendered moot and respectfully request that the Examiner reconsider and withdraw the rejections.

In view of all of the above comments, Applicants submit that the claims pending in this application are now in proper form for allowance. Accordingly, the Examiner is respectfully requested to enter the amendments, withdraw the rejections, and pass Claims 9-13, 20, 37-56, 58-75, 112-116, and 121-129 to allowance.

Respectfully submitted,

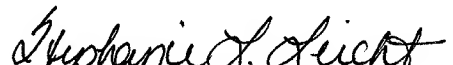


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Stephanie L. Leicht